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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	

NOTIFICATION DATE	DELIVERY MODE
07/08/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/341,894	PIECHACZYK ET AL.	
	Examiner	Art Unit	
	MAGDALENE K. SGAGIAS	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,53,55 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-53, 55 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 4/7/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 52-53, 55 and 60 are pending and under consideration. Claims 1-51, 54, and 56-59 and 61 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-53, 55 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotypic response directed against said antibody in said mammal, said method comprising transplanting into said mammal a genetically modified mammal cell which comprises a polynucleotide comprising: (i) a nucleotide sequence encoding an antibody or fragment thereof to be delivered by said genetically modified mammal cell when transplanted into said mammal; (ii) a promoter sequence controlling expression of the nucleotide sequence from (i) in the genetically modified cell; and (iii) an element ~~guaranteeing~~ providing the secretion by the genetically modified cell when transplanted into said mammal of the encoded antibody or fragment thereof, wherein said polynucleotide is expressed and the genetically modified cell secretes when transplanted into the subject mammal the encoded

antibody or fragment thereof such that the antibody or fragment thereof reaches the blood circulation of the subject mammal; wherein said cell is a cell not specialized for the production of antibodies, which has the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from the subject mammal or from another mammal, which is a compatible donor; and wherein an anti-idiotypic response is not triggered.

The specification teaches that C2C12 cells genetically modified with mouse anti-human thyroglobulin monoclonal antibody (Tg10) and which retained the capacity to differentiate into myotubes in vitro were implanted via injection in the forelegs of syngenic C3H mice and the production of recombinant antibodies having retained the thermodynamic properties, and the recognition property of the initial antibody antigen was followed for two months (specification example 6). The specification teaches the quantity of antibody produced was regularly elevated from the base level to a production of approximately 100 ng/ml of serum (specification, example 6). The specification also contemplates that one of the essential goals of the invention is to systemically produce a recombinant antibody, beneficially therapeutic by genetically modified mammalian cells [0091-0091]. The specification teaches that a possible risk of this approach is the induction of an immune response on the part of the modified organism capable of neutralizing the recombinant antibody [0095]. The specification also discusses that this potential problem was avoided in the experimental results presented in their example 6 primary myogenic cells expressing a stable Tg10 monoclonal antibody after retroviral transduction were implanted at the level of the tibialis anterior of the C3H mouse [0096] and the quantity of Tg10 antibody secreted was dosed with the ELISA method and in parallel, the quantity of anti-idiotype antibody was determined by ELISA [0093-0096]. The specification discusses that no anti-idiotype response could be detected under these conditions [0097]. While the specification teaches that in said mice the quantity of the antibody was monitored by ELISA and no anti-

idiotypic response could be detected under these conditions, however, the specification fails to provide guidance to correlate the levels of the Tg10 antibody produced to the lack of an induced anti-idiotypic response and moreover, wherein said transduced cell is capable of differentiating into a tissue but retains the ability to secrete the antibody, and furthermore wherein said secreted antibody in the blood is a therapeutic antibody at therapeutic levels. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating any the diseases disclosed in the specification by way of the claimed method. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

At the time of the instant invention the art of transplantation of ex vivo genetically engineered cells, for the production of antibodies by a genetically engineered ectopic cell (that is a cell other than a B cell) comprising a transgene encoding for an antibody and then transplanting said cell in a mammal, resulting in the expression and secretion of the antibody in vivo, wherein an anti-idiotypic response is not triggered was unpredictable without undue experimentation. With regard to cell-based gene therapy in vivo, while progress has been made in recent years, cell transfer, homing and expression of a transgene at therapeutic levels without triggering an anti-idiotypic response to the transgene continuous to be a difficulty s supported by teachings in the art. The art of allogeneic or xenogeneic cell antibody-mediated gene/cell therapy is an unpredictable art with respect to the survival of non-antibody producing cells (that is ectopic antibody producing ***cells***) in vivo, levels of recombinant antibody produced after transplantation, in vivo. **Qu et al,** (The Journal of Cell Biology, 142: 1257-1267, 1998) at the time of the instant invention reports the application of cell and gene therapy in combination is facing major hurdles (p 1258, 2nd column, last paragraph). Qu reports through the combination of myoblast transplantation and gene therapy, the ex vivo gene transfer approach has been

investigated as a gene delivery approach in the skeletal muscle and both the ex vivo procedure and the myoblast transfer approach are limited by the poor survival of the injected myoblasts (p 1258, 2nd column). Qu also reports the origin of the myogenic cells may influence their survival (abstract).

The specification teaches the transplantation of C2C12 cells genetically modified with mouse anti-human thyroglobulin monoclonal antibody (Tg10) into syngeneic mice. **Hortelano et al,** (Haemophilia, 7: 207-214, 2001) notes that microcapsules enclosing recombinant C2C12 myoblasts genetically engineered with the transgene for secreting human factor IX after transplantation into mice even though said cells delivered the transgene into the plasma of mice as determined by ELISA, however tumors rended to appear after 6 weeks and Hertelano notes that this cell line is notorious for inducing tumorogenicity and probably the antibody levels detected before the onset of tumors at week 4 were not secreted by the tumors (p 212, under discussion). As such it is not clear the Tg10 antibody detected after two months of the transduced C2C12 myoblasts in the instant invention is secreted by tumorigenic C2C12 cells.

Bendandi (Leukemia, 14: 1333-13339, 2000) notes that idiotypes are located in the hypervariable regions of the immunoglobulin (Ig) variable domain, and are recognized as being foreign due to the fact that the tiny quantity present in any individual is insufficient to induce self tolerance (p 1333, 1st column, 2nd paragraph). Furthermore, the differences between donor and recipient idiotypes may be functionally relevant in the context of B cell function regulation (Bendandi et al, p 1333, 1st column, 2nd paragraph). The disclosed example 6 in the specification provides general guidance for producing an antibody in a subject, however fails to address any issue regarding any immune response(s) and antibody production in said subject to the production of a foreign antigen, in this case a recombinant antibody, wherein an anti-idiotypic response is not triggered against the recombinant antigen. Therefore, the skilled

artisan would conclude that the state of art of transplantation of genetically engineered cells with a gene encoding an antibody in vivo, wherein an anti-idiotypic response is not triggered is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating any of the disclosed diseases by way of the claimed method without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for transplanting a genetically engineered cell ex vivo for ectopic antibody production in vivo, without triggerring an anti-idiotypic response, the lack of direction or guidance provided by the specification for transplanting a genetically engineered cell ex vivo for ectopic antibody production in vivo, without triggering an anti-idiotypic response, the absence of working examples that correlate to the treatment of a disease, by way of the claimed method, the unpredictable state of the art with respect to ectopic antibody production in vivo after transplantation of a genetically engineered cell ex vivo, and in particular without triggering an anti-idiotypic response to the produced antibody, the undeveloped state of the art pertaining to the treatment of a disease by way of the claimed method, and the breadth of the claims directed to all diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue the claimed method is not a method of treating disease X or providing therapeutic levels of antibodies in a mammal. The claimed method is simply to delivering an antibody. There cannot be any dispute that the application as originally filed enables delivering an antibody following the method steps defined in the claims. Applicants argue the claimed method is directed to a novel generic mode for administration of monoclonal antibodies (mAbs), which is independent of the nature of the administered antibody. Similarly, the development of a

new syringe would be independent of the molecules that it would contain when used to treat patients. The main point of the invention is to demonstrate that a monoclonal antibody can be produced by genetically- modified non-B cells in a living mammal and that this mAb can be distributed systemically, as shown by its presence in the blood circulation, without inducing significant adverse against the mAb, i.e., inducing an anti-idiotypic response capable of neutralizing it (see the Examples).

In response to applicant's arguments, the recitation of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotypic response directed against said antibody in said mammal has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In this case, the claims as interpreted in view of the teachings in the specification are not enabled because the specification teaches the use of the ectopic expression of an antibody in vivo for treating diseases. For example, the specification teaches the invention concerns the use of a nucleic acid sequence containing an antibody gene and elements guaranteeing the expression in vivo of said antibody gene and the secretion in the blood circulation of a mammal of a therapeutically effective quantity of this antibody or a fragment of it, by cells of said mammal genetically modified by said nucleic acid sequence and not naturally producing antibodies, for the preparation of pharmaceutical compositions for treating mammals by gene transfer [0060]. More specifically, this use targets the preparation of pharmaceutical compositions for treating cancer or viral infections [0060]. Applicants have failed to provide guidance for such an effect in

vivo. These arguments are not persuasive because as discussed above applicant's findings that CH3 mice produced the ectopic Tg10 antibody in vivo without eliciting an anti-idiotypic response cannot overcome the issues of unpredictability of the claimed methods. Because the expression of the ectopic antibody in vivo via transplantation of the myoblasts C2C12 cells it doesn't necessarily mean that injection of the Tg10 transduced cells by any route and at any dose will home into target cells in vivo resulting in a sufficient expression of the transgene to treat the diseases disclosed in the specification cells as claimed in the instant application. The MPEP only states the examiner cannot ask for clinical trial data regarding safety or efficacy for enablement. No such requirement is in the present record. Applicant's claims encompass producing ectopic antibody in vivo via transplantation of transduced cells ex vivo via transplantation of said cells by any route of administration of the cells in vivo. Applicants have not shown such an effect in vivo.

Applicants argue the Examiner's reliance in the rejection of producing a "therapeutic" level of an antibody is misplaced because the claimed method is directed to a method of delivering an antibody into a subject and if it is done the way it is claimed, one will produce an antibody via transplantation of non-B cells producing the antibody and no anti-idiotypic response will be triggered. The method does not require treating a disease with this antibody similar to a new syringe that delivers a substance into a subject without a requirement to treat a disease, if any, in the subject with this substance. To answer the Examiner's assertion regarding unpredictability, in the description of the invention, the inventors resorted to (i) a model antibody (Tgl0) presenting a number of advantages (e.g., mouse origin, cloned and characterized in the laboratory, availability of a very sensitive ELISA, availability of methods to study a possible anti-idiotypic response against it, which is extremely rare, availability of reliable methods to assess

its thermodynamic and kinetic properties in complex biological fluids such as serum) to prove the concept and (ii) vectors, expression cassettes and grafting procedures.

These arguments are not persuasive because a) it is not predictable that an antibody will produced in vivo via transplantation of non-B cells producing the antibody in vitro and b) via the transplantation of xenogeneic or allogeneic transduced cells by way of the claimed methods. This is because as discussed above the art of allogeneic or xenogeneic cell antibody-mediated gene/cell therapy is an unpredictable art with respect to the survival of non-antibody producing cells (that is ectopic antibody producing cells) in vivo, levels of recombinant antibody produced after transplantation, in vivo. **Qu et al,** report the application of cell and gene therapy in combination is facing major hurdles as for example, the combination of myoblast transplantation and gene therapy, the ex vivo gene transfer approach has been investigated as a gene delivery approach in the skeletal muscle and both the ex vivo procedure and the myoblast transfer approach are limited by the poor survival of the injected myoblasts and the origin of the myogenic cells may influence their survival.

Applicants argue concerning the latter point, vectors, expression cassettes and grafting procedures used by the inventors were known and amongst the most efficient and widely used ones at that time. Applicants argue obtaining a nucleotide sequence encoding an antibody, cloning the sequence into an expression vector using a known promoter and elements providing secretion of the antibody, and transplantation techniques are well known in the art. Using these tools, the inventors have demonstrated the feasibility of the systemic delivery of mAbs keeping their functional properties in a living mammal through genetic ex vivo modifications of non-B cells (i.e., cells not naturally producing antibodies) that could be used in gene/cell therapy protocols.

These arguments are not persuasive because the issue is not the construction of expression cassette vectors or the ex vivo modification of non-B cells rather the issue is the production of functionally therapeutic levels of ectopic antibody production in vivo via ex vivo modifications of non-B xenogeneic and/or allogeneic non-B cells. For example, the specification teaches syngeneic transplantation of non-B cells genetically modified ex vivo produce antibodies in vivo of the transgene, as evidenced by its thermodynamic properties. However, the thermodynamic properties of the expressed Tg10 antibody are not creatable to therapeutic levels of the Tg10 antibody in the mouse with a disease. As discussed above, **Bendandi** notes that idiotypes are located in the hypervariable regions of the immunoglobulin (Ig) variable domain, and are recognized as being foreign due to the fact that the tiny quantity present in any individual is insufficient to induce self tolerance. Furthermore, the differences between donor and recipient idiotypes may be functionally relevant in the context of B cell function regulation. The disclosed example 6 in the specification provides general guidance for producing an antibody in a subject, however fails to address any issue regarding any immune response(s) and antibody production in said subject to the production of a foreign antigen, in this case a recombinant antibody, wherein an anti-idiotypic response is not triggered against the recombinant antigen but the antibody retains a functional therapeutic effect. The thermodynamic characteristics of the produced antibody cannot be correlated with a therapeutic effect as is the intended use of the claimed method. Therefore, the skilled artisan would conclude that the state of art of transplantation of genetically engineered cells with a gene encoding an antibody in vivo, wherein an anti-idiotypic response is not triggered is undeveloped and unpredictable at best.

Applicants argue concerning Hortelano et al., the authors implanted C2C12 cells producing factor IX into mice with the aid of micro-capsules. They then found that tumors had appeared after 6 weeks. Thus, the question is one of finding out whether, in the present application, the antibody is produced by non-tumorous cells after two months and not by tumorous cells. In order to encapsulate the C2C12 myoblastic cells secreting factor IX, Hortelano et al. used alginate capsules. This involves tiny spheres made from a substance extracted from alga. The cells are trapped within. However, this substance is not very solid and disintegrates quite rapidly. This explains why C2C12 cells escaped and were able to produce tumors in some animals. Hortelano et al. conducted experiments on nude immuno-deficient mice, whereas Applicants' experiments were conducted on non-immuno-compromised mice. These were syngeneic in order to prevent any rejections of grafted cells. Nude mice are among the most sensitive in- vivo methods used to test the tumorigenicity of tumorous cells (and indeed to preserve tumors that prove impossible to replicate under usual cell-culture conditions). Thus, it is entirely logical that tumors appeared rapidly in these animals. By contrast, the C3H mice of the present applications do not all develop tumors when grafted with C2C 12 cells, and when tumors do occur, they cannot be detected before 3-4 months under the experimental conditions Applicants used. This gives an ample time to assess whether the gene or cell therapy works. Moreover, if antibody production were associated with proliferating tumorous cells (and not the muscle, which fails to proliferate following fusion of myoblasts with resident muscle fibers), it is likely that Applicants would have seen an increase in the concentration of the Tgl0 mAB (linked to the increase in the number of productive cells) in their animals, as a function of time. This was not the case. As stressed by Hortelano et al., C2C12s cells are known to be tumorigenic. However, this did not preclude C2C 12s from being among the best cell systems at the time of

the invention to facilitate muscle formation after grafting to histo-compatible mice (grafted myoblasts fuse rapidly with resident muscle fibers to create muscle).

These arguments are not persuasive because as discussed above the antibody produced by the CH3 mice of the present application even though, the produced Tg10 antibody in vivo elicited no anti-idiotypic response, Applicants failed to provide guidance of a therapeutic use of the claimed method. Moreover, Applicants failed to provide guidance for such an effect before the induction of a potential tumor by the transplanted C2C12 myoblasts transduced with the Tg10 transgene.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The

examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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